Complete Summary

GUIDELINE TITLE

Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Yu E, Lochrin C, Dixon P, Ung YC, Gagliardi A, Evans WK. Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Sep [online update]. 25 p. (Practice guideline; no. 7-12). [34 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Locally advanced, unresectable, stage III non-small cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To determine if any altered fractionation radiation schemes prolong survival in the treatment of locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) compared with the North American standard of 60 Gy in 30 fractions

TARGET POPULATION

Patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

Altered Fractionation Radiation Schemes:

1. Hyperfractionated radiation therapy (non-accelerated)
2. Accelerated radiation therapy
3. Hyperfractionated accelerated radiation therapy (HART) and variants, including continuous hyperfractionated accelerated radiation therapy (CHART) and continuous hyperfractionated accelerated radiation therapy weekendless (CHARTWEL)
4. Hypofractionated radiation therapy
5. Split-course radiation therapy, including:
    - Standard total treatment dose at 1.8 to 2.0 Gy fraction size, but with different total treatment time and an interruption interval of one to two weeks
    - Standard total treatment dose, but different fraction size to maintain the same overall treatment time including the interruption interval of one to two weeks
    - Different total treatment dose, fraction size, overall treatment time and interruption interval

MAJOR OUTCOMES CONSIDERED

Primary Outcome

- Survival

Secondary Outcome

- Toxicity/side effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1999 Guideline

The MEDLINE (Ovid) database was searched from January 1987 to July 1999 and the CANCERLIT (Ovid) database from January 1987 to April 1999 using these terms: carcinoma, non-small cell lung; radiotherapy; hyperfractionation; accelerated fractionation; hypofractionation; altered fractionated; randomized controlled trial; meta-analysis; and guidelines. The Physician Data Query file (PDQ; U.S. National Cancer Institute) and the Cochrane Library (1999, Issue 2) were also searched to identify clinical trials.

2002 Update

The original literature search has been updated using MEDLINE and CANCERLIT (through September 2002) and the Cochrane Library (through Issue 4, 2002) databases and the 2002 proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology.

Inclusion criteria

Articles were selected for inclusion if they met the following criteria:

1. Randomized controlled trials comparing altered fractionation (including continuous hyperfractionated, accelerated, continuous hyperfractionated accelerated radiation therapy [CHART], hyperfractionated accelerated radiation therapy [HART], continuous hyperfractionated accelerated radiation therapy weekendless [CHARTWEL], or hypofractionated and split-course radiotherapy) with conventional fractionation in the treatment of stage III non-small cell lung cancer.
2. Comparative cohort studies and phase I/II studies were eligible where data from randomized controlled trials were not available.
3. Survival was the primary outcome of interest. Toxicity was also considered.

NUMBER OF SOURCE DOCUMENTS

12 documents

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

A published meta-analysis (fixed effects Peto model) of three randomized controlled trials comparing standard fractionation radiotherapy to hyperfractionated radiotherapy was identified. The Cancer Care Ontario Practice Guideline Initiative's Resource Group conducted a meta-analysis (unpublished) of two-year survival data from the same three randomized controlled trials (fixed effects Peto model) using the software application Meta-analyst[0.988] provided by Dr. Joseph Lau, Tufts New England Medical Centre, Boston, MA. Results were expressed as an odds ratio for deaths, with a 95% confidence interval. Pooling of data could not be performed for any other altered fractionation strategy due to lack of published randomized controlled trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Based on the evidence described in the original guideline report, the Lung Disease Site Group (DSG) drafted recommendations.

The Lung DSG´s concerns about the meta-analysis published by Stuschke and Thames were addressed through consultation with Dr. G. DeBoer (biostatistician from the University of Toronto) and suggestions from Dr. G. Browman. The Lung DSG recognized that there were insufficient data (or data of uncertain quality) for the acceptance of hyperfractionated radiation as the new standard of treatment in patients with locally advanced non-small cell lung cancer (NSCLC). The odds ratios determined by the two meta-analyses were very similar (0.69 and 0.67). Although the significance levels were similar, one did not quite reach the conventional level of statistical significance ($p=0.09$), while the other did ($p=0.02$). Because these results were not very robust to minor differences in method, and given the major implications to treatment centres of switching from conventional to hyperfractionation schedules, the DSG did not feel that the strength of the evidence was sufficient to support a recommendation away from conventional practice towards hyperfractionated therapy.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 98 practitioners in Ontario (46 medical oncologists, 26 radiation oncologists and 17 surgeons and the heads of radiation oncology programs at the eight regional cancer centres and the Princess Margaret Hospital). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Lung Cancer Disease Site Group.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Key Recommendations

- There is evidence from one randomized controlled trial demonstrating that continuous hyperfractionated accelerated radiation therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC). Selected patients (with Eastern Cooperative Oncology Group [ECOG] performance status $\geq$ 1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for continuous hyperfractionated accelerated radiation therapy.
- Evidence from a comparative cohort study suggests that hyperfractionated accelerated radiation therapy (HART) also improves survival over standard radiotherapy.
- Of those trials designed to improve therapeutic ratios in patients with locally advanced, unresectable stage III non-small cell lung cancer there is insufficient data of high quality to recommend hyperfractionation over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of hyperfractionation radiotherapy.
- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III non-small cell lung cancer did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life or health care costs was not reviewed in most of these trials. Therefore, if quality of life and health care costs are

issues of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

One published meta-analysis, eight randomized controlled trials, one comparative cohort study and two randomized phase I/II trials evaluating altered fractionation (including continuous hyperfractionated, accelerated, continuous hyperfractionated accelerated radiation therapy [CHART], hyperfractionated accelerated radiation therapy [HART], continuous hyperfractionated accelerated radiation therapy weekendless [CHARTWEL], or hypofractionated and split-course radiotherapy) were reviewed.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- These guidelines may aid physicians in choosing an appropriate radiotherapy regimen for their patients with locally advanced, unresectable stage III non-small cell lung cancer.
- The published meta-analysis demonstrated a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.95; p=0.02). The Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Resource Group conducted an (unpublished) meta-analysis of the same trials as the published meta-analysis which did not demonstrate a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.67; 95% confidence interval, 0.42 to 1.07; p=0.091).
- Three of four randomized controlled trials demonstrated a survival benefit for hyperfractionation compared with standard radiotherapy, although not all results were statistically significant (data from one of the three trials were not statistically significant; data from the second trial demonstrated a three year survival rate of 22% for hyperfractionated versus 0% for standard radiotherapy, but no significance level was reported; and the third trial demonstrated a statistically significant two-year survival benefit [p<0.05]).
- With respect to hyperfractionated accelerated radiotherapy: one randomized controlled trial which compared CHART with standard radiotherapy demonstrated an advantage with CHART for two-year survival rates (30% versus 21%) and five-year survival rates (20% versus 13%) (hazard ratio, 0.78; 95% confidence interval, 0.65 to 0.94; p=0.008). One comparative cohort study demonstrated a three-year survival benefit for hyperfractionated accelerated radiation therapy (HART) of 28% versus 6% for standard radiotherapy (p<0.001). No survival data were cited in the full report of one phase I/II study of continuous hyperfractionated accelerated radiation

therapy weekendless (CHARTWEL); the authors state that there was no survival difference between the two groups at 18 months after radiotherapy.
- One randomized controlled trial showed that hypofractionation improved three-year survival (19% versus 9% for standard radiotherapy) but no significance was reported. Acute treatment toxicity was reduced in the hypofractionation patients (30% experienced no esophagitis compared with 70% of standard radiotherapy patients).

POTENTIAL HARMS

- Acute esophagitis is the main adverse effect associated with all of the altered fractionated radiotherapy regimens.
- Hyperfractionation, continuous hyperfractionated accelerated radiotherapy (CHART) and hypofractionated radiotherapy demonstrated no significant differences in late toxicity compared with standard radiotherapy. Esophagitis was more severe ($p=0.004$) and of longer duration ($p<0.0001$) in patients receiving accelerated radiotherapy compared to the standard radiotherapy group. Esophagitis was experienced by 87% of hyperfractionated accelerated radiation therapy (HART) patients versus 44% of standard radiotherapy patients ($p<0.05$). Accelerated radiotherapy was shown to increase acute toxicity over standard radiotherapy. It is unclear whether toxicity was monitored for split-course radiotherapy.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Yu E, Lochrin C, Dixon P, Ung YC, Gagliardi A, Evans WK. Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Sep [online update]. 25 p. (Practice guideline; no. 7-12). [34 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Oct 8 (revised online 2002 Sep)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group Members

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Lung Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2002. The information was verified by the guideline developer as of July 8, 2002. This summary was updated by ECRI on June 23, 2003. The updated information was verified by the guideline developer on July 16, 2003.

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